TUMOURS

The role of chemotherapy in the treatment of bone and soft tissue sarcomas

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Summary While surgery remains the cornerstone of treatment of bone and soft tissue sarcomas, chemotherapy has improved the 5-year overall survival in osteosarcoma and Ewing’s sarcoma from 10% to 70% in localized disease. Patients with metastases at presentation treated with surgery combined with chemotherapy have a 3-year survival of 30–50%, but cure is still rare. The role of adjuvant chemotherapy in soft tissue sarcoma has yet to be determined, but it is likely that some patients will benefit. As some bone sarcomas do not respond to chemotherapy, surgery remains the only effective treatment, and there are no effective drugs to treat relapsing patients. Radiotherapy has both a curative role in combination with chemotherapy in soft tissue and Ewing’s sarcoma and a palliative role in the other sarcomas.

KEYWORDS
Sarcomas; Bone; Soft tissue; Chemotherapy

Bone sarcomas

Primary malignant bone tumours represent 0.2% of newly presenting cancers. The different histotypes are related to the original cell (Table 1). The most common bone sarcomas are: osteosarcoma 45%, chondrosarcoma 22%, and Ewing’s sarcoma 15%. Osteosarcoma and Ewing’s sarcoma have shown dramatically improved cure rates since the introduction of adjuvant (postoperative) and neo-adjuvant (preoperative) chemotherapy. Chondrosarcoma and chordoma do not respond to chemotherapy.

Osteosarcoma (OS)

Osteosarcoma is classified:

- High Grade Central OS
  - Fibroblastic
  - Osteoblastic
  - Chondroblastic
  - Telangiectatic
- Low Grade central
  - Grade 1
  - Grade 2
Parosteal/periosteal (low malignancy)

Secondary OS (to Paget’s disease, irradiated bones).

It is a high grade malignant spindle cell tumour arising within bone and histologically characterized by production of ‘tumour’ ‘osteoid’ or immature bone directly from the malignant spindle cell stroma. It is the most frequent type of malignant bone tumour, with an annual incidence of about 3 new cases per million. It occurs mainly in childhood and adolescence with a median age of 16. When it occurs over 40 years of age, it is usually associated with pre-existing bone diseases. Ten percent of cases occur in patients over 60. Males are affected more commonly than females, ratio 1.6:1.0.

At presentation osteosarcoma is localized in 80% of cases while metastases are present in about 20%.7 75% are in the appendicular skeleton, arising in the metaphysis of long bones. Lung is the most common metastatic site, followed by bone.

Unfavourable prognostic indicators are:

- male gender
- primary tumour in the pelvis or axial skeleton
- poor tumour necrosis (<90%) after preoperative chemotherapy
- tumour volume
- elevated serum alkaline phosphatase
- inadequate surgical margins
- metastatic disease.

Metastatic disease at presentation is the most important unfavourable prognostic factor. Disease Free Survival (DFS) is 70% in localized disease, but falls to 20–30% in cases of metastatic disease even after combined treatment. Thus low grade (1–2), periosteal and parosteal osteosarcoma that metastasise slowly have an overall survival of 75–85% with surgery alone.

To understand current best practice, it is necessary to understand how current treatments developed. Until the 70’s osteosarcoma was treated by amputation alone*. Despite good local control, most patients died due to pulmonary metastases. The 5-year DFS was 12%, and 3 out of 4 patients died within 2 years of diagnosis. In the early 70’s adjuvant chemotherapy following surgery was introduced, the aim being to kill micrometastases that had already spread at diagnosis, even in

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**Table 1** Different histotypes of bone sarcomas and treatment-sensitivity.

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Malignant bone tumor</th>
<th>Chemo-sensitive</th>
<th>RT-sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteogenic</td>
<td>Classic osteosarcoma</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Small cell osteosarcoma</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Multifocal osteosarcoma</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chondrogenic</td>
<td>High grade chondrosarcoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Dedifferentiated chondrosarcoma</td>
<td>Y/N</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Mesenchymal chondrosarcoma</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Nervous</td>
<td>Ewing’s sarcomas</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Primary neurectodermal tumours</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Histiocytic</td>
<td>Malignant fibrous histiocytoma</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fibrous</td>
<td>Fibrosarcoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Smooth muscular</td>
<td>Leiomyosarcoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Notocordal</td>
<td>Chordoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vascular</td>
<td>Hemangiendothelioma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Hemangiopericytoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lipogenic</td>
<td>Liposarcoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mixed</td>
<td>Malignant mesenchymoma</td>
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<td>No</td>
</tr>
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<td>Hematopoetic</td>
<td>Multiple myeloma</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

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apparently localised disease. The first protocols included high doses of methotrexate (MTX) or Doxorubicine (DOX) or the two combined. The 5-year DFS rose to between 40% and 60%. Other chemotherapeutic agents were added (Vincristine, Bleomicine, and Dactinomycin) but abandoned due to poor effectiveness. However the subsequent addition of Cisplatin (CDP) and Ifosfamide (IFO) to DOX and MTX led to further improvement in the 5-year DFS (70%).

After 1983, neoadjuvant (preoperative) chemotherapy was introduced and the DFS reached a 70–75%. Neoadjuvant chemotherapy, in addition to eradicating micro-metastases, was intended to destroy the primary tumour cell. Reduction of the tumour bulk would permit more limb sparing surgery, from 10% to 95%. An additional benefit of neoadjuvant chemotherapy was a prognostic evaluation based on tumour necrotic response to chemotherapy permitting identification of postoperative chemotherapies. Currently neoadjuvant treatment protocols for osteosarcoma aim to:

- increase the percentage of healing
- further reduce mutilating surgery
- reduce toxicity.

Drugs
Currently MTX, DOX, CDP and IFO remain the mainstays of treatment. It must not be forgotten that in almost all adjuvant and neoadjuvant chemotherapy protocols for osteosarcoma, there have been deaths due to drug toxicity.

*Methotrexate.* MTX is only effective when used in high doses. However there is great individual variation in the metabolism of MTX, and recent neoadjuvant protocols tailor the dosage of MTX to each patient, based on blood levels after the first cycle with 12 g/m².

*Doxorubicin.* DOX if used as a single agent in OS has a response rate of about 30%. Cardiotoxicity is its main side effect and cardiomyopathy can be manifest many years after treatment. Nonetheless, as significant benefits accrue from an early use of this drug and as the risk of DOX cardiotoxicity correlates with the cumulative dose of the drug, more recent protocols use reduced dosages by 24 h infusion rather than single bolus.

*Cisplatin.* In current preoperative protocol with 4 drugs (MTX, CDP, DOX, IFO), intra-arterial administration of CDP does not offer any advantages. Intravenous infusion over 48 or 72 h rather than over 5 h has the same effect with less neurologic and renal toxicity.

*Ifosphamide.* IFO is the latest drug used to treat osteosarcoma. Recent protocols include high dose IFO together with the other drugs. Currently we use IFO (15 g/m²) over 5 days for patients who relapse.

Adjuvant or neoadjuvant chemotherapy?
Is neoadjuvant chemotherapy for OS, used for many years, still appropriate? As reconstructive endoprostheses are readily available, and chemotherapy can be started 4–5 days after surgery, delay before surgery is not necessary. Neo-adjuvant chemotherapy given for several weeks before surgery runs the risk of leaving un-operated a drug resistant tumour, with subsequent selection of chemo-resistant clones that can metastasize.

The only relevant controlled study was by the Pediatric Oncology Group between 1986 and 1993. Patients were randomized to adjuvant or neoadjuvant groups, receiving the same chemotherapy regimen with MTX-CDP-DOX-BCD. The number of amputations, DFS, and overall survival were the same in the two groups.

We believe that treatment should be individually tailored. There is advantage to be gained from neoadjuvant chemotherapy for an easily resectable lesion (e.g. of the fibula), but a large OS of the humerus, at limit of resectability, could greatly benefit from neoadjuvant chemotherapy as lesions preoperatively treated with chemotherapy are more easily operable than untreated tumours. Current neoadjuvant protocols have a 5-year DFS range between 61% and 76%. Two problems remain, what is the best treatment for patients with distant metastases at presentation, and what is the best treatment for patients who relapse?

Primary metastatic osteosarcoma
About 20% of all osteosarcomas are metastatic at presentation. Current practice is aggressive treatment with chemotherapy and surgery of the primary tumour and all metastases. In our series, none of the patients with both bone and lung metastases achieved remission. The number of lung metastases was a significant prognostic factor: all patients with less than 5 nodules were disease free after treatment, but only 40% of those with more than 5 lung nodules. At a mean follow up of 4 years (2–7) only 7 (20%) of the 36% pts who achieved remission remained disease free. The 2-year DFS for the group of 36 pts who reached a disease-free status after treatment was 38% (28% in those with only lung metastases, 0% otherwise). The COSS study, reported similar results. Despite aggressive treatment, the prognosis of osteosarcoma metastatic at presentation is still poor. Survival is related to the number and location of metastases.
and completeness of surgical resections of all tumour sites.

Also patients with multifocal bone disease at presentation have an extremely poor prognosis, but systemic chemotherapy and aggressive surgical resection may achieve significant prolongation of life.9

**Treatment of metastatic relapsed osteosarcoma**

Despite chemotherapy and surgical resection, 30–40% of patients with local osteosarcoma of extremities relapse. Recurrence is most common in the lungs. Complete resection of recurrent disease is the most important prognostic factor at first relapse with a 3/5-year survival rate of 20–40% following resection of metastatic pulmonary tumours.10 Prognosis is better with less than 4 nodules, and with a longer disease free interval. The prognosis for patients who develop bone metastases or local recurrence is even worse. Surgery for metastases is still the best accepted strategy, while the role of second-line chemotherapy is not well defined yet, because all the most effective drugs are used in neo-adjuvant chemotherapy.

**New experimental drugs**

Peripheral blood stem cell transplant utilizing high dose chemotherapy does not seem to improve outcome.11 High dose samarium-153-EDTMP may provide significant pain control in patients with bone metastases.

Other drugs undergoing trial include Gemcitabine with Docetaxel. Correlation of HER2 expression with unfavourable prognosis has led to a trial of Herceptin. Ecteinascidin-743 in combination with other drugs is subject to an ongoing trial. Encouraging results were reported in localized osteosarcoma with a combination of Muramyldipeptide, (derivative of the BCG cell wall, with immunostimulation activity) together with IFO and standard therapy. CDP, MTX and DOX.

**Ewing's sarcoma**

Ewing's sarcoma (ES) is the second, most common, primitive malignant tumour of bone after osteosarcoma. It represents the 3% of all malignant paediatric tumours; 90% of patients are aged less than 20 years with a peak incidence at 14 years.

Histologically, ES comprises a group of small round cell tumours of neuro-ectodermal origin. It arises in bone marrow or soft tissue (when in the chest wall it is called Askin tumor). ES can be distinguished immuno-histochemically from other paediatric 'blue tumors' by expression of MIC2 gene. ES is an aggressive disease with a high mortality. About 25% of patients have clinically apparent metastases at presentation. Lung is the most common site of metastases followed by bone and bone marrow. However, 20–30% of those with apparently localized disease have a micro-metastatic disease in bone marrow, detectable by molecular techniques such as PCR. This correlates with poor outcome. Unfavourable prognostic factors are:

- metastatic disease (patients with bone metastases have worst overall survival)
- elevated serum LDH level at presentation
- poor histologic response to induction chemotherapy
- tumour in axial skeleton.

Overall survival at 5 years has improved from 10–15% to 60–70% with chemotherapy combined with local treatment (surgery and/or radiotherapy).

**Treatment for localized disease**

Standard therapy for localized ES includes pre-operative induction chemotherapy (4–5 cycles), and local treatment with surgery and/or radiotherapy. ES is very radiosensitive; radiotherapy alone is used for large tumours where surgery is not feasible (e.g. vertebra, pelvis) and may be used post-operatively if surgical margins are inadequate. Subsequently, 10–22 weeks of chemotherapy are given for consolidation. The aim is local control and the eradication of micro-metastases.

Drugs used in the 1970s were DOX, Cyclophosphamide (CIFO) and Vincristine (VCR) +/– Dactinomycin (DAC), combined (VACD). With these 4 drugs, the 5-year DFS was 30–60%.

Latterly, IFO and Etoposide (ET) have been added to most protocols as they show synergistic activity and increased DFS to 60–70% and OS to 80%. The introduction of granulocyte colony-stimulating factors (GCSF) has allowed increased drug dosage without toxicity. Increased dosage may increase DFS and OS, but tailoring treatments to histologic response, tumour volume and site is essential.

Surgery gives better DFS than radiotherapy alone, but radiotherapy is often the choice for large volume axial bone tumours with a worse prognosis anyway. We compared12 the role of surgery and radiotherapy in 268 patients with non-metastatic Ewing’s sarcoma localized to an extremity. The results, supported by other studies, suggest that surgery is the best option, at least for
limb ES. Postoperative radiation therapy must be added in case of inadequate margins.

**Treatment of metastatic disease and relapses**

The prognosis of metastatic disease is still poor especially for bone metastases but as many as one third with only lung metastases achieve remission with conventional combined multimodal treatment (chemotherapy, surgery, radiotherapy). Most protocols use the same drugs (VCR, DOX, IFO, CIFO, ET, DAC) used in localized disease but at higher doses with GCSF support or PBSC Rescue as increased dose was thought to improve the fraction of tumour cells killed, but results were not good. This regime often includes a myeloablative consolidation treatment with megatherapy with or without total body irradiation. The rationale for total body irradiation is the eradication of micrometastases, and it has been used in high-risk patients as a part of a multimodal treatment with systemic chemotherapy, but in the majority of studies it did not increase survival and it increased toxicity. Myeloablative megatherapy with alkylators such as Melphalan and Busulphan in patients with bone or bone marrow metastases have shown good results. Lung radiotherapy is indicated for patients with lung metastases, in remission after chemotherapy, with consolidation purpose.

**New experimental drugs**

Topoisomerase I inhibitors are a new class of anticancer drugs. Early experience showed modest activity when used alone, but better when used in combination with alkylators. Irinotecan+Temozolamide showed some activity in heavily pretreated pediatric solid tumors.

**Other bone tumors**

*Small cell osteosarcoma:* A rare variant of osteosarcoma resembling Ewing's sarcoma, but with a worse prognosis. Treatment is as for osteosarcoma.

*Radioinduced osteosarcoma:* A late complication of radiotherapy treatment arising in previously irradiated fields. It is associated with higher doses of radiotherapy (>40 cGy) and with a latency of 5–20 years. Treatment is the same as classic osteosarcoma.

*Chondrosarcoma:* The second most common primary malignant tumour of bone. There are five types of chondrosarcoma:

- central
- peripheral
- mesenchymal
- dedifferentiated
- clear cell

The 10-year survival with peripheral is 77% vs 32% for central lesions. Chondrosarcomas are not chemosensitive and surgery is the main therapy. An exception is mesenchymal chondrosarcoma which is highly aggressive with a 10-year survival of less than 30% so adjuvant chemotherapy is recommended. 10% of chondrosarcomas dedifferentiate into osteosarcoma or fibrosarcoma requiring chemotherapy.

*Malignant fibrous histiocytoma:* Chemosensitive and can benefit from adjuvant chemotherapy.

**Soft-tissue sarcomas**

Adult soft-tissue sarcomas account for 0.7% of all cancers. They arise from primitive mesoderm and in any extra-skeletal connective tissue, in the extremities (50–60%), trunk and retroperitoneum (30–40%), or head and neck (10%). A small percentage arise in the gastrointestinal tract—gastrointestinal stromal tumors.

They are classified histologically, but each type can behave as benign to local recurring or highly malignant. The current staging system is based on the main prognostic factors: histologic grade, size, and depth of the tumour (relative to the superficial fascia). They have an intermediate chemosensitivity. Hence a surgically based multi-disciplinary treatment is necessary for optimum results. Where surgery is difficult or not feasible (e.g. retroperitoneal or trunk tumours) results are poor. Latterly there have been attempts to improve local control.

The role of chemotherapy in metastatic disease is unclear. Patients with high-risk lesions seem to benefit from adjuvant or neoadjuvant chemotherapy. For metastatic disease, various drugs have been tested as single agent or combination regimes, but results in terms of response rate and overall survival are often contradictory. Newer drugs and improved knowledge of the biology of these tumours could help in the definition of more targeted therapies for this heterogeneous group of diseases.

**Adjuvant chemotherapy**

It is difficult to assess the role of adjuvant chemotherapy because the first generation of
clinical trials included small numbers of patients, with different tumor histologies, grade and location, treated with different drugs at different doses. The Sarcoma Meta-Analysis Collaboration Group (SMAC) collected the data from 14 randomized clinical trials and showed a small survival benefit of 4% overall at 10 years for the treatment group (not significant, $P = 0.12$), increasing to 7% ($P = 0.029$) for extremity lesions. The absolute benefits in local relapse-free interval, distant relapse-free interval, and overall recurrence-free survival were respectively 6%, 10%, and 10% in favor of chemotherapy.

Later trials (after 1990), indicated that DOX and IFO are the most active agents in soft tissue sarcomas. The study from the Italian Sarcoma Group compared local treatment alone with local treatment plus five cycles of epirubicin and IFO the absolute benefit deriving from chemotherapy was 13% at 2 years and increased to 19% at 4 years ($P = 0.04$).

### Neo-adjuvant chemotherapy

As with bone tumours, neo-adjuvant therapy offers many advantages, particularly shrinkage of tumour mass, improving the chances of limb/organ salvage, and may permit radical surgery in initially inoperable tumours. It also allows assessment of the tumour to chemotherapy. Despite the theoretical advantages, there is no evidence that neo-adjuvant chemotherapy is better than an adjuvant approach in terms of DFS, and overall survival but response to neo-adjuvant treatment is a prognostic factor for local disease control. This is true for radiographic response and for histologic response as well.

#### Table 2 Combination chemotherapy in metastatic STS.

<table>
<thead>
<tr>
<th>Institute/study</th>
<th>No pts</th>
<th>Type pts</th>
<th>Drug</th>
<th>Dose (mg/m²)</th>
<th>RR (CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb</td>
<td>275</td>
<td>advanced</td>
<td>A+D</td>
<td>60</td>
<td>47%</td>
</tr>
<tr>
<td>Borden et al.</td>
<td>105</td>
<td>advanced</td>
<td>MAID</td>
<td>A 69, I 7500, D 900</td>
<td>47% (10%)</td>
</tr>
<tr>
<td>Elias et al.</td>
<td>140</td>
<td>advanced</td>
<td>CyVADIC</td>
<td></td>
<td>50% (17%)</td>
</tr>
<tr>
<td>Schoenfeld et al.</td>
<td>200</td>
<td>advanced</td>
<td>A</td>
<td>A 70</td>
<td>27%</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td>VAdriC</td>
<td>V 1.4, A 70, Cy 50</td>
<td>19%</td>
</tr>
<tr>
<td>Antman et al.</td>
<td>340</td>
<td>untreated</td>
<td>A+D</td>
<td>A 80</td>
<td>17%</td>
</tr>
<tr>
<td>Intergroup</td>
<td></td>
<td>metastatic/unresectable</td>
<td>ADI</td>
<td></td>
<td>32%</td>
</tr>
<tr>
<td>Edmonson et al.</td>
<td>262</td>
<td>advanced</td>
<td>A</td>
<td>A 60, I 7500</td>
<td>20%</td>
</tr>
<tr>
<td>Santoro et al.</td>
<td>663</td>
<td>...</td>
<td>A</td>
<td>A 70</td>
<td>23.3%</td>
</tr>
<tr>
<td>Steward</td>
<td>104</td>
<td>...</td>
<td>A</td>
<td>750 A50/I5</td>
<td>28.1%</td>
</tr>
<tr>
<td>Le Cesne</td>
<td>294</td>
<td>...</td>
<td>A+I+GM-CSF</td>
<td>75/5</td>
<td>45% (10%)</td>
</tr>
</tbody>
</table>

A = Doxorubicine, D = Dacarbazine, I = Ifosfamide, Cy = Cyclofosfamide, V = Vincristine, Act = Actinomycin-D, MAID = mesna, doxorubicine, ifosfamide, dacarbazine, ADI = MAID, MAI = mesna, doxorubicine, ifosfamide, MAP = mitimycin-C, doxorubicine, cisplatin, CyVADIC = Cyclofosfamide, vincristine, doxorubicine, dacarbazine.
Recurrent and metastatic disease

Relapse is common within two to three years from diagnosis. Retro-peritoneal sarcomas tend to have local recurrence at higher rates. Distant relapse is more frequent to the lungs (20% of patients), less to bone (7%), liver (4%), and lymph nodes (less than 4%). Myxoid liposarcoma of the extremity tends to metastasize to the abdomen and pelvis. If possible, salvage treatment both for local and distant recurrence is radical re-excision with or without radiotherapy. In patients with less than four lung metastases and no endobronchial invasion, and after a long disease free interval, complete pulmonary resection can give long-term survival in 15–40%. While chemotherapy remains an option for inoperable patients with metastatic or recurrent disease, the response rates in Stage IV soft tissue sarcoma have been low.

Drugs

**Doxorubicine:** The first drug that showed activity in metastatic soft tissue sarcoma with a response rate of 20–30% when administered as single agent.

**Cyclophosphamide:** It is inactive as a single agent and after a randomized controlled trial has been replaced by ifosfamide.

The studies on combination chemotherapy in metastatic soft tissue sarcoma are shown in Table 2.

New agents

Gemcitabine has shown activity in several types of tumours including soft tissue sarcomas. Other newer agents include docetaxel and paclitaxel. Liposomal DOX is a new form of DOX in which the drug is encapsulated in liposomes aiming to reduce toxicity, in particular cardiotoxicity and myelosuppression. It has equivalent activity to standard DOX, and should be considered for those patients who are at risk of greater cardiotoxicity.

Ecteinascidin-743 (ET-743): A novel marine-derived antineoplastic agent. Preclinical and initial clinical data have shown an activity of the compound, alone or in combination with cisplatin, paclitaxel and DOX, in some type of tumours, such as breast and ovarian cancer, and soft tissue sarcomas.

No responses have been reported for GISTs, while best responses were seen in patients with leiomyosarcoma and liposarcoma.

Conclusions

Adjuvant or neoadjuvant chemotherapy, with Doxorubicine+Ifosfamide regimens in conjunction with radiotherapy is recommended for patients presenting with large (>5 cm), intermediate- or high-grade tumours. For untreated metastatic patients a combination of surgery (always recommended when feasible) and DOX-IFO based chemotherapy can be used for palliative purposes and is able to prolong survival.

References

patients treated by megatherapy (MGT) and stem cell reinfusion (SCR) in Europe. Proceedings of the ASCO; 1999. p. 2144.